EXHIBIT 71

Amide Pharmaceutical, Inc.
101 East Main Street
Little Falls, NJ 07424
EI: 11/15-19, 23, 24, 29, 12/1/04 EDM

SUMMARY OF FINDINGS

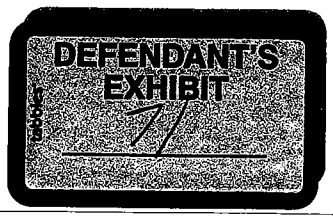
A cGMP inspection of this generic prescription pharmaceutical manufacturer was conducted as per New Jersey District workplan, FACTS assmt. 2484291, op. id. 1984475. A pre-approval inspection of ANDA 76-689, Mirtazapine Orally Disintegrating (OD) Tablets, 15mg, 30mg and 45mg and coverage of DQRS and NDA Field Alert reports were also conducted. Compliance programs 7356.002, Drug Manufacturing Inspections, 7346.832, Pre-approval Inspections/Investigations and 7356.021, Drug Quality Reporting System (DQRS), NDA Field Alert Reporting were used for guidance.

The previous inspection of 9/3/04 et. al. was classified NAI for follow-up to failed CDER surveillance samples of Hyoscyamine Sulfate Modified Release Capsules. The previous cGMP and preapproval inspection of 3/24/03 was classified VAI. Deficiencies were cited regarding performance qualifications for laboratory and manufacturing equipment used for the preapproval product. Promised corrective actions were verified during the current inspection.

The current inspection covered six systems and a preapproval for ANDA 76-689, Mirtazapine OD Tablets, 15mg, 30mg, and 45mg. The following deviations were noted: changes were not consistently reviewed, approved and evaluated by the Quality Unit to determine the impact on marketed product or filing requirements; Quality Control laboratory supervisors who review and approve data had administrative access to the computerized systems which permits alteration, deletion, renaming and relocating of raw data files; Research and Development products were manufactured on commercial manufacturing equipment in the absence of cleaning validation studies or cleaning verification after every batch; production documentation was stored in common corridors, accessible to employees and contractors when not in use and was not controlled in a manner to prevent alteration or removal; approximately 25% of commercial manufacturing equipment has not been qualified for its intended use; specifically two conical blenders and a tablet press used to manufacture ANDA 76-689, Mirtazapine OD Tablets were not qualified. An FDA 483, Inspectional Observations was issued 12/1/04 to Divya Patel, President. All profiles are acceptable and a recommendation for approval of ANDA 76-689 was faxed to New Jersey District Preapproval Manager. A profile sample was collected for ANDA 76-689 as CR# 68868. No refusals were encountered during the inspection.

ADMINISTRATIVE PROCEDURES

On 11/15/04, we, Investigators Erin D. McCaffery and Robert C. Horan, Ph.D. issued an FDA 482, Notice of Inspection **(Att)** to Divya Patel, President. We presented credentials, a copy of "Resources for FDA Regulated Businesses" and stated the purpose of our inspection. Dr. Horan participated in the inspection as an auditor only. Mr. Patel and Jasmine Shah, R.Ph., Director Regulatory Affairs notified us at the initiation of the inspection that the site was working on a "skeleton crew" due to a large percentage of the employees celebrating the Indian New Year. However, Mr. Shah stated that the site was open for sales and business and that they could accommodate us. He stated that the facility would be fully operational on 11/16/04.



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On 12/1/04 an FDA 483, Inspectional Observations **(Att)** was issued to Divya Patel, President following discussions with management. Mr. Patel stated that the firm would respond in writing to New Jersey District Office with planned corrective actions for all observations.

On 12/1/04 an FDA 484, Receipt for Samples **(Att to CR# 68868)** was issued to Jasmine Shah, R.Ph. for a profile sample collected for ANDA 76-689, Mirtazapine OD Tablets (CR# 68868).

The inspection was conducted by Investigator McCaffery on 11/15-19, 23, 24, 29 and 12/1/04. Dr. Horan observed the inspection on 11/15-19/04. This Establishment Inspection Report was written entirely by Investigator McCaffery. All references to the first person are referring to Investigator McCaffery.

PERSONNEL INTERVIEWED

An organizational chart was provided as **Exh. 1.** The following firm personnel provided information and documentation during the inspection:

Divya Patel, President was present at the initiation of the inspection to accept the FDA 482, Notice of Inspection, periodically throughout the inspection to review history of business and operations, and at the closeout meeting to accept the FDA 483, Inspectional Observations. Mr. Patel became the President of the company following the passing of his father, Chandu Patel in 4/03. Divya Patel was formerly the Vice President of Sales and Marketing.

Ashok Nigalaye, Ph.D., Vice President Scientific Affairs was present periodically throughout the inspection. He discussed a centralized document control system and the potential use of new technology for analysis of cleaning validation samples. He was present at the exit meeting and discussed the difficulty in qualifying older equipment. Dr. Nigalaye reports to Divya Patel, President.

Jasmine Shah, R.Ph., Director Regulatory Affairs facilitated the inspection and provided all documentation and information requested. Mr. Shah acts as the contact to New Jersey District Office. He conducted walk throughs of the facility, described history of business and operations, described planned changes for facilities and personnel, discussed complaint handling, adverse event reporting, finished product release, corrective actions, product history, and the pre-approval product. Mr. Shah was with the company prior to the Consent Decree and has historical knowledge of the operations. Mr. Shah reports to Dr. Nigalaye.

Frank Carlucci, Ph.D., Director Quality Control oversees the Analytical Development and Quality Control laboratories. He provided an overview of laboratory operations including testing of raw materials, in-process and finished products and stability samples. He described equipment qualification, work assignment, Departmental Operating Instructions (DOIs), change control procedures, investigations, review and approval of data, reference standard qualification, Turbochrom, and employee training. Dr. Carlucci reports to Dr. Nigalaye.

Mark Tenny, Director Manufacturing Operations has only been with the company for approximately three months. He replaced Michael Plaviak who retired. Mr. Tenny was present during some of the production walk throughs and was present at the closeout meeting. Mr. Tenny reports to Dr. Nigalaye.

Ashesh Dave, Director Packaging Operation facilitated that walkthrough of the packaging area and described blister and bottling operations, inventory control, shipping, controlled substance storage, brite stock, quarantined stock, and returned goods. Mr. Dave reports to Dr. Nigalaye.

Daniel Bitler, Director Quality Assurance was transitioned into his current position for approximately six months following the departure of his predecessor, Ken Weaver. Mr. Bitler was introduced during the inspection and was present during the exit meeting. He reports to Dr. Nigalaye.

Manoj Patel, Director Engineering was formerly a full time employee, but currently is only on site approximately one day per week. Mr. Patel is the administrator of the computerized systems and discussed security of the operating system, Windows NT and the chromatography software, Turbochrom via teleconference. Mr. Patel reports to Divya Patel, President.

Satish Laroia, Director Manufacturing Compliance was present briefly during the inspection. He provides in-house training for manufacturing employees. He was present at the exit meeting on 12/1/04.

Nilesh Patel, Supervisor Quality Control Laboratory is one of three Quality Control Laboratory Supervisors. He provided general information during the inspection of the laboratory and demonstrated the use of Turbochrom including the audit trail. He discussed investigations and described Departmental Operating Instructions. Mr. Patel conducted the weighing of each of the sub samples required for the collection of the profile sample. He also provided information and explained the raw data and notebooks for finished product and stability testing for ANDA 76-689, Mirtazapine Orally Disintegrating Tablets. Mr. Patel reports to Dr. Carlucci.

Chandu Patel, Supervisor Quality Control assisted during the walkthrough of the laboratory on 11/15/04. He retrieved logbooks and notebooks and discussed reference standard storage and usage. He is one of three supervisors in the Quality Control Laboratory and reports to Dr. Carlucci.

Dmitriy Kalika, Information Technologist described the computerized systems utilized for generation of analytical data. He discussed the security of the Windows NT operating system and the Turbochrom software. He generated screen shots which detailed personnel security privileges and system capabilities. Mr. Kalika has administrator access in Windows NT and acts as a system administrator for the site when Manoj Patel is not on site. Mr. Kalika reports to Manoj Patel, Director Engineering.

Varsha Bhagat, Label Room Coordinator described the receipt and use of labeling, reconciliation, use of the label counting equipment, quality review of labeling, and the

procedures for receipt, issuance and return of labeling. Varsha Bhagat reports to Ashesh Dave, Director Packaging Operation.

Manubhai Patel, Compression Operator discussed the manufacture of Digoxin Tablets. Manubhai Patel reports to Kirit Patel, Supervisor Compression.

HISTORY OF BUSINESS/OPERATIONS

Amide Pharmaceutical, Inc. is a privately held, family owned organization which has been in operation since 1983. Divya Patel, President, stated that the company has undergone significant changes, especially following the Consent Decree of Permanent Injunction in 1992. The site was shut down for one year in 1992. The Consent Decree was lifted in 2001 following successful demonstration of sustained cGMP compliance. Jasmine Shah, R.Ph., Director Regulatory Affairs facilitated the current inspection. Mr. Shah noted two changes in management since the last inspection due to retirement **(Exh. 1).** Ken Weaver, Director Quality Assurance was replaced by Daniel Bitler. Mr. Bitler was transitioned into the position for six months prior to Mr. Weaver's departure. Michael Plaviak, Director of Manufacturing also retired and was replaced approximately three months ago by Mark Tenny. Mr. Patel explained that they are trying to develop expertise in mid-level employees between the Director and Supervisor level through hiring and training. He stated that no other management changes have occurred since the last inspection.

The firm specializes in prompt and sustained release solid oral dosage forms for smaller output products. They maintain 36 ANDA products and also manufacture 50 DESI products **(Exh. 2).** Approximately 640 batches were manufactured in 2004. The facility is 61,000 square feet including the 21,000 square foot packaging facility located on the same property approximately 20 yards from the main facility. The main facility consists of 18,000 square feel for manufacturing, 5,500 square feet for the Quality Control Laboratory, 9,500 square feet of office space/cafeteria, and 7,000 square feet of warehouse space. There are 183 personnel currently employed at the site. The site operates from 7:30-4:30 Monday through Friday with overtime until 6:00 p.m. as needed. A Saturday shift from 7:00-3:00 is used as needed. Maintenance is conducted after routine production hours or on the weekend. Mr. Shah stated that there is always a Director present for all production shifts. The firm has another facility at 4 Taft Road, Totowa, NJ and is in the process of moving all packaging and Analytical Research and Development to that facility. CBE 30s have been filed for all of the ANDA products and DESI products have already been transferred to the other site for packaging. All transfers will be completed by late December according to Mr. Shah. The Analytical Research and Development Laboratory at Taft Road has also been qualified for QC purposes to serve as a backup laboratory if needed by the Little Falls, NJ site. All non-controlled substance finished products manufactured at the Little Falls, NJ site will be warehoused and shipped from the Taft Road, NJ facility. A list of controlled substances utilized at the site and their associated finished products was provided as **Exh. 3.**

Mr. Patel notified us that there is a larger facility located at 990 Riverview Drive, Totowa, NJ that is being retrofitted for production; however it is in the early stages and is not planned for completion until approximately 2006. Mr. Shah stated that there are approximately 100 products with the Amide label **(Exh. 2).** Other products are

manufactured and private labels are applied for such companies as Johnson and Johnson, Warner Chilcott, Sanofi, Qualitest, Watson and Bertek. He stated that they contract manufacture several products such as Rifampin Capsules USP 300mg for Sandoz, Inc.; prescription prenatal vitamins, Natachew and Natafort Tablets for Warner Chilcott; urinary tract analgesics, Pyridium Plus Tablets for Warner Chilcott; Phenazopyridine HCl Tablets for ACP; and Nicomide Tablets for Sirius Laboratories. The product list includes the number of batches manufactured each year for 2003 and 2004 as well as the application numbers (if filed) and the indications for use **(Exh. 2).** During the walkthrough we observed the construction of manufacturing suites for two sustained release, sugar coated over-the-counter products, Drixoral Cold and Allergy Tablets and Chor-Trimeton Tablets, which will be contract manufactured for Schering Plough following approval. The deadline for operations in the newly renovated portion of the facility is 12/15/04 according to Mr. Shah. The site already conducts sugar coating for Phenazopyridine Tablets, but will expand with an additional 7 sugar coating pans in order to contract manufacture the new products.

Mr. Shah stated that there are no rework or reprocessing procedures for any product. He stated that the only modification that can be made to a finished product is to repackage it into a different packaging configuration based on customer orders. Rejected products are logged and periodically removed by Specialty Disposal Services for witnessed incineration in Hempstead, Long Island, New York. Chem Tech is contracted for pest control services at the facility and a report is provided to management.

There are two systems for documenting problems at the facility; the first is deviations in the production area and the second is out-of-specification results. Mr. Shah provided log books for each of the two types of events and selected investigations were reviewed.

There are two types of procedures: Standard Operating Procedures (SOPs) and Departmental Operating Instructions (DOIs). Both are handled through the documentation system. Quality Assurance maintains the electronic versions if modifications are needed, however the hard copy is the official document which is signed. Departments train and manage their own DOIs; however Quality Assurance has 5 employees responsible for review, modification and approval of SOPs (Vice President Scientific Affairs, Director Quality Assurance, Director Manufacturing, Director Regulatory Affairs, Director Quality Control).

Facility diagrams are provided as **Exh. 4.** Operations including granulating, blending, drying, milling, compression, encapsulation, and packaging/labeling were observed. All raw materials are weighed in the room where they will be used for manufacturing. There is no pharmacy weighing area at the facility. Equipment used includes but is not limited to pony mixers, conical blenders, V blenders, tablet presses, encapsulators, coating pans, sugar coating pans, capsule polishers, tablet printers, drying ovens, bottle and blister packaging equipment. All tablet presses are gravity fed and all drying is conducted using tray dryers. Mr. Shah stated that they intend to upgrade to fluid bed drying and more automated operations when products are moved to the newer facilities. A comprehensive list of equipment at the facility is provided as **Exh. 5.**

A list of consultants currently providing services to the site is included as **Exh. 6.** Areas in which consulting is being used includes equipment qualification at the new Taft Road facility, cGMP training and compliance, Quality Control training, and bio-study review (on an as needed basis). A list of all CBEs and Prior Approval Supplements was requested and provided **(Exh. 7).** Mr. Shah provided a list which predominantly consisted of CBEs to change packaging locations to Taft Road, Totowa, NJ.

FIELD ALERT REPORTING

A final Field Alert Report for NDA 40-282, Digoxin Tablets 0.25mg was filed during the reporting period **(Att).** It was submitted to New Jersey District Compliance Branch on 8/16/04. The initial report from a pharmacist, dated 5/17/04, described a "thick tablet" from lot# 3611A, expiration date 12/04. New Jersey District Compliance Branch was notified by the site and the investigation was completed at the time of inspection. The final Field Alert Report noted that the "most probable cause" of the thick tablet was that the tablet was manufactured during setup and became stuck in the deduster, but was not detected or removed prior to the start of commercial production. Procedural enhancements were made to include more documented steps to verify the removal of all setup tablets for all tablet products. Training was also conducted. No additional complaints or reports of thick tablets have been received for this high volume product. The event was considered an isolated incident and corrective actions were put in place to prevent its reoccurrence. Corrective actions (procedural enhancements and review of complaint files) were verified during the inspection.

DESI AND GRANDFATHERED PRODUCTS

Mr. Shah provided a list of DESI/grandfathered products that are manufactured at the site **(Exh. 2).** Review of the labeling revealed that some of the products have extended release formulations. I collected labeling **(Exh. 8)** which describes the release pattern of the products. I discussed with Mr. Shah and Mr. Patel that by definition, DESI/grandfathered products do not have extended or sustained release patterns. Mr. Patel stated that they have followed the industry regarding such products and have discontinued the manufacture of any products which they once considered DESI or grandfathered, but have since been required to file an application, such as Guaifenesin ER Tablets. Mr. Patel explained that they discontinued manufacturing Guaifenesin ER Tablets following receipt of an industry wide Warning Letter. He stated that it is not cost effective to file applications for older small volume products. He explained that he and his competitors routinely manufacture such products without applications, considering them grandfathered, but stated that Amide will comply with any FDA initiated directives, similar to Guaifenesin.

DISCONTINUED PRODUCTS

Two products were discontinued during the reporting period according to Mr. Shah. He noted that Hyoscyamine Sulfate 0.375mg ER Capsules were discontinued due to the testing issues identified during CDER surveillance testing and the follow-up inspection. He stated that the product on the market met specifications at the time of release and will continue to be monitored on stability; however no new batches will be manufactured at this time. The second product, Guaifenesin ER Tablets was discontinued in 2/03

following the receipt of an industry wide Warning Letter requiring an application for the extended release product.

REFUSALS

No refusals were encountered during the inspection.

RECALLS

There were no recalls during the reporting period.

STABILITY OUT-OF-SPECIFICATION RESULTS

Review of stability data and investigations revealed that one stability out-of-specification result has been obtained in the last two years. On 11/6/02, an out-of-specification result was obtained for related substances at the 12 month CRT condition for Quinapril Hydrochloride/Hydrochlorthiazide Tablets 20mg/25mg, lot# RBR-1105. Investigation revealed that the analyst retained the initial tablet grind used for assay testing in a bag for several days before performing the related substance testing. As a result, the related substance results were out-of-specification. Review of the method revealed that it only specifies that the sample should be analyzed within 2 hours of preparation, but does not indicate that the tablet grind should be made fresh for each analysis. As a result, clarification was added to the methodology and the original results were disqualified due to the assignable cause. Mr. Shah confirmed that no other stability out-of-specification results were obtained during the reporting period.

PREAPPROVAL COVERAGE OF ANDA 76-689, MIRTAZAPINE ORALLY DISINTEGRATING TABLETS, 15mg, 30mg, and 45mg

The product was originally developed by Kali Laboratories, Inc., Piscataway, NJ. An interim development report dated 2/27/02 **(Exh. 9)** was provided and describes the development and subsequent transfer to Amide Pharmaceutical, Inc. The report explains that the product was developed to match the in-vitro characteristics and be bioequivalent to Remeron® Sol-Tab manufactured by the innovator, Organon, Inc. The product was formulated in a dose proportional manner to the innovator's product.

The product is manufactured via wet granulation in a low-shear mixer. The granulation is oven dried and then Fitz milled. The milled in-process material is blended with sweetener, flavor, Pharmaburst® and Crospovidone. It is lubricated with talc and Magnesium Stearate and then compressed into tablets. The active ingredient, Mirtazpine, is hygroscopic and light sensitive. It is purchased from Sumika Fine Chemicals, Co., Ltd. (represented in the U.S. by Byron Chemicals, Co., Inc.) A bioequivalence study was conducted by AAI, Chapel Hill, NC. A summary of the research batches manufactured in support of the development and transfer is provided in the interim development report written by Kali Laboratories, Inc. **(Exh. 9 pp. 12-15)** Mr. Shah stated that the first research batch completely processed at Amide according to Kali's formulation was RBR 1198 (3 kilos) on 3/25/02. The 10,000 tablet batch was 15mg strength. Additional master blend batches were identified as RBR 1247 (13.5

kilos) and finally 1294 (220 kilos), which was used for the submission batches. An Amide Product Development Summary Table was also provided as **(Exh. 18).**

The site had not manufactured validation batches at the time of inspection. There are two batch sizes filed; 220 kilos (submission batch) and 1000 kilos (never manufactured). They currently have approval for the manufacture of Mirtazapine Tablets, but filed ANDA 76-689 for the orally disintegrating formulation. The product is manufactured utilizing a common granulation. The submission batches, RBR 1295 (15mg), RBR 1299 (30mg) and RBR 1300 (45mg) were manufactured from RBR 1294, a 220 kilo common granulation batch. The executed records for the common granulation (1294), and the three finished dosage lots 1295, 1299, and 1300 are provided as **Exhs. 10-13.** The common granulation was manufactured 6/13/02 and the 15mg, 30mg, and 45mg batches were manufactured 6/17/02, 6/18/02 and 6/22/02 respectively. The submission batches were manufactured with a 2% overage, however follow a deficiency letter from CDER, the overage was removed and future batches will not be manufactured with an overage. Specifications for release and stability testing are provided as **Exh. 14.** Raw data was reviewed and verified for 15mg, 30mg, and 45mg stability samples at the 4 week room temperature, 6 month accelerated, and 26 week accelerated time points, respectively. Stability summary tables were also provided which contain acceptable 24 month controlled room temperature data in both 30 count bottles and blister packs **(Exhs. 15-17).** We discussed the impurity specifications for release and stability. The specification for chromatographic purity for the degradant MTZNO is 0.1% for the finished product and 1.0% on stability. Review of the data revealed that the highest value observed for MTZNO for the 24 month stability data was 0.439% for batch# RBR 1299 (30mg, CRT) **(Exh. 17).** Additionally, the total known and unknown impurity specification is set at 1.5% on stability, which is also unsupported by the limited data available as the highest value obtained was at 24 months (30mg, CRT) at 0.663% **(Exh. 17).** I requested justification for the setting of the specification because the limited stability data available did not support the proposed specification. Mr. Shah stated that they had just received another deficiency letter and the reviewer had also requested changes for the specifications. He stated that they were evaluating the data, but would propose 0.8% instead of 1.0% for MTZNO on stability and would subsequently be revising the total impurity specification. Mr. Shah stated that the consistency in our findings further supported the need for change.

No investigations were conducted during manufacturing or testing of the three submission batches. A list of all raw materials, the supplier's name and lot number were provided for RBR-1295 (15mg) **(Exh. 18 p. 2),** which was collected as a profile sample (CR# 68868) **(Att).** Equipment qualification was reviewed for the intended commercial manufacturing operations and found to be deficient for the 32 cubic foot and 112 cubic foot conical blenders as well as the Stokes B2 16 station tablet press used for the manufacture of the finished tablets. (See FDA 483 observation 6.) No other deviations were noted for the product and recommendation for approval was faxed to New Jersey District Preapproval Manager.

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SAMPLES COLLECTED

A profile sample (CR# 68868) **(Att)** consisting of 11 sub samples was collected for ANDA 76-689, Mirtazapine Orally Disintegrating Tablets. The sample was prepared at New Jersey District Office and shipped to FDA's Forensic Chemistry Center on 12/9/04.

COMPLAINTS

There is one complaint handling system which is overseen by Jasmine Shah, Director Regulatory Affairs. Mr. Shah explained that all complaints are forwarded to Regulatory Affairs. Quality complaints and adverse events are all reported into the manual log of complaints. Mr. Shah, a registered pharmacist, reviews all incoming complaints to determine the appropriate course of action. A list of all complaints since 10/03 was provided **(Exh. 19).** The list contained approximately 9 complaints for 4 different lot numbers of cracked Amidirine Capsules (41 lots manufactured in 2003-2004). Of the nine complaints, three were reported through DQRS reports, (MSB#s 2004-02278, 2004-01344, and 2004-01259). The defect was described as the red portion of the capsule shell cracking. At the time of inspection, an investigation was completed and corrective actions were implemented. A determination was made that the product's formulation was hygroscopic and was absorbing water from the moisture sensitive capsule shell causing it to dry and crack in some cases. As a result, the capsule shell manufacturer was contacted and a replacement for the capsule shell was found. The product was put on stability; however it is considered a "DESI" product for Amide and therefore has no filed application. Mr. Shah stated that the change was documented through change control as part of the annual product review. No additional complaints were obtained following the change. Mr. Shah stated that review of their retain samples did not confirm the cracked capsule shells, however due to the product complaints and investigation findings, corrective actions were made. He stated that all product which is returned will be replaced. We discussed the varying environments and differences in the sealed bottle (retains) versus a bottle which has been used repeatedly in a pharmacy and exposed to varying environments. Documentation for shipments of returned goods were reviewed for the cracked capsule complaints. I observed the product being packaged during a walkthrough and verified that the capsule shell had been changed.

A larger number of complaints was also noted for Digoxin Tablets, however it is the highest volume product (179 batches manufactured in 2003-2004) according to the list of batches produced per year **(Exh. 2).** There were also no trends observed for the types of complaints. I requested any trending of the data for complaints and was told that although the complaints are reviewed periodically and for the annual product review, there is no formalized trending for complaints. Mr. Shah stated that due to the growth of the company, they would evaluate trending for complaints and other quality indicating metrics. No deviations were noted upon review of timeliness or completion of complaint follow-ups or investigations.

Complaint 24455 from SAN-DO

FDA Complaint# 24455 **(Att)** was received by SAN-DO. It was noted in FACTS as in-progress, but was received 4/5/04. The Consumer Complaint Coordinator was contacted and follow-up was conducted at Amide, the New Jersey manufacturing site

during the current inspection. Review of the complaint log revealed that Amide was not notified by the complainant. The complaint was for the DESI product, Amidrine Capsules. It was unknown whether the complainant requested confidentiality, so limited information was provided to the firm. Concurrence was obtained from New Jersey District supervision and Compliance Branch to notify the firm of the drug name due to the associated adverse event (excessive diuresis, headache and "hypertension") noted by the complainant. Mr. Shah reviewed the complaint log and found no other occurrences of the same type of complaint in the history of the product. He stated that it would be logged in their complaint file; however we were unable to provide enough information to complete a MedWatch form due to the confidentiality issues. CDER will be contacted directly for notification of the adverse event for this DESI product. Mr. Shah stated that if any additional information is provided by the complainant or FDA, he will process the adverse event. A copy of the package insert **(Exh. 20)** was reviewed for Amidrine Capsules and the adverse events do not appear to be labeled.

Drug Quality Reporting System (DQRS)

The following 7 DQRS reports were provided by the New Jersey District DQRS monitor for follow-up **(Att).**

1. **MSB File Number 2003-02821 (Confidentiality NOT requested)**
   Betaxolol Hydrochloride Tablets USP 10mg, lot# unknown, exp. 4/05.

   The products potency was questioned following elevated blood pressure after switching to Amide's product from Kerolone 10mg for blood pressure control. The complainant reported that upon returning to Kerolone, her blood pressure returned to normal. The complaint was logged as Amide complaint C03-035 **(Exh. 19)** and follow-up was completed as per procedures.

2. **MSB File Number 2004-00327 (Confidentiality WAS requested)**
   Clidinium Bromide/Chlordiazepoxide Capsules 2.5mg/5mg, lot# 3362A2, exp. 7/31/06

   This report was not provided to the site by CDER or during the inspection due to the confidentiality request. Review of the complaint log for 2003-2004 revealed that there were no complaints for the product. Twenty-nine batches have been manufactured in 2003-2004.

3. **MSB File Number 2004-02204 (Confidentiality NOT requested)**
   Carisoprodol Tablets USP 350mg, lot unknown, exp. Unknown

   Potency was questioned for Carisoprodol Tablets. The complainant claimed that no follow-up was provided. The complaint was logged as Amide complaint C04-033 **(Exh. 19)** on 7/6/04 and the follow-up was completed 7/16/04. No deviations were noted upon investigation.

4. **MSB File Number 2004-02137 (Confidentiality NOT requested)**
   Quinaretic (Quinapril HCl and Hydrochlorothiazide Tablets), lot# 4179A1, exp. 10/30/05

Conflicting information was provided in the DQRS report regarding the manufacturer; however the complainant stated that human hair was found inside the bottle on top of the cotton. The complaint was logged as Amide complaint C04-020. It was received 6/5/04 and completed 6/8/04. No deviations were noted.

The last three DQRS reports were identified in the complaint log as C04-005, C04-006, and C04-036. Corrective actions for the cracked capsule shell were completed prior to this inspection as documented above in the "COMPLAINTS" section of this report. No deviations were noted in the complaint investigations conducted for C04-005, C04-006, and C04-036.

5. **MSB File Number 2004-02278 (Confidentiality NOT requested) Amidrine Capsules, lot# 3590A1, exp. 10/05**

   The capsules were split longitudinally and powder came out of the capsules. The pharmacy stock bottle also had all split capsules. The complaint was logged as Amide complaint 04-036. The investigation was completed as described in the "COMPLAINTS" section of this report.

6. **MSB File Number 2004-01344 (Confidentiality WAS requested) Amidrine Capsules, lot# 3590A1, exp. 10/05**

   The site had received this report and it was logged as complaint 04-006. The investigation was completed 3/7/04 and deviations were addressed as described in the "COMPLAINTS" section of this report.

7. **MSB File Number 2004-01259 (Confidentiality WAS requested) Amidrine Capsules, lot# 3636A1, exp. 11/05**

   The site received this report and it was logged as complaint 04-005. The investigation was completed 3/7/04 and deviations were addressed as described in the "COMPLAINTS" section of this report.

DISTRIBUTION

According to Jasmine Shah, Director Regulatory Affairs, distribution is documented through a manual card system. He stated that the system is very simplistic and allows for quickly identifying all customers to whom the product was distributed. Although the manual card system has been working successfully since the inception of the firm, they recognize that due to growth, it is time to consider a computerized, more advanced system. Released finished product was formerly distributed from the Little Falls, NJ site. However, all non-controlled substances will now be stored at the Taft Road, NJ facility and will be distributed from there. Controlled substances will remain at Little Falls, NJ for distribution due to storage requirements. Released product is distributed on a "First In, First Out" (FIFO) basis. A manual stickering system is used for all materials in the facility to identify their status as quarantine or on-hold, released, on-

test, or rejected. Further, quality checks are conducted to verify that only released material is picked for distribution.

SYSTEMS COVERED

This inspection was conducted as a Level II performance audit for Investigator McCaffery. Robert Horan, Ph.D., CSO New York District conducted the audit. Inspection of the facility therefore required the coverage of six systems: Quality, Laboratory Control, Facilities and Equipment, Production, Packaging and Labeling, and Materials. All items highlighted in the compliance program were evaluated from 11/15-19/04. General areas of coverage included, but were not limited to investigations into out-of-specification results, manufacturing deviations, complaints, field alert reporting, recalls, returned goods, rejected materials, training, production and analytical trending, validation, cleaning, change control, computerized systems, release of product, qualification of vendors, receipt of raw materials, label control, manufacturing including packaging and labeling, analytical testing including stability, retain sample maintenance, written procedures (DOIs and SOPs), equipment qualification and calibration, containment in a multi-use facility and distribution of product to the market.

DISCUSSIONS WITH MANAGEMENT

During the inspection the following items were discussed with management:

- There is currently no vendor auditing program in place at the site. Mr. Shah stated that vendor auditing was not conducted due to resource constraints. We discussed the need to confirm through both auditing and testing that the APIs, excipients, components and other vendor supplied items are manufactured in a manner that is deemed acceptable by Amide and according to cGMP. We discussed quality agreements with suppliers to assure that Amide is notified of changes and the need to try to reduce risk for materials manufactured outside their control. Mr. Shah stated that they would like to establish a program, but would need to discuss it further with management.

- On two occasions during a facility walkthrough on 11/15/04, the room cleaning and use logbooks for the quarantine sampling area **(Exh. 21)** and compression room 115 **(Exh. 22),** did not represent the current status of the room. In the quarantine sampling area, the log indicated that the room had been cleaned and inspected; however upon observing the sampling area there was white powder remaining on the floor and no evidence that the room had been cleaned. On 11/16/04 Mr. Shah confirmed that the room was not cleaned prior to the employee's departure for the long weekend. He stated that the cleaning should not have been documented until after its completion. The compression room (115), which contained clean covered equipment was used 10/25-27/04 for manufacturing Vitaplex Plus Tablets, batch 4604A, but had not been cleaned following manufacturing according to the equipment cleaning and use log for the tablet press (equip. id. 75). Mr. Shah stated that it was also a mistake to put the clean equipment into the unclean room. He said that the responsible employees would be notified and all equipment in the room would be recleaned. We discussed the need to accurately document all activities at the time of occurrence.

- We observed employees manually screening raw materials in a production room with portions of their arms exposed to the product between their gloves and uniform sleeves. The direct contact with the raw materials was discussed with management. An immediate corrective action was made during the inspection to require employees to wear sleeve covers during manufacturing.

- We discussed the need for additional, more detailed information in the annual product reviews. Digoxin Tablets, 0.125mg Annual Product Review, dated 3/23/04 **(Exh. 23),** is provided as an example. There is currently no listing of specific complaint types, product defects, production or analytical trending or evaluation of the validated status of the product. Discrepancies were observed in the number of complaints reported for the two strengths of Digoxin. Mr. Shah stated that Dan Bitler, Director Quality Assurance also noted the deficiencies in reporting when he joined the company approximately six months ago. Mr. Shah committed to review and enhancement of Annual Product Reviews.

- We discussed more frequent calibration of the equipment used to measure total organic carbon for the water system. The current practice is to evaluate it monthly. Mr. Shah provided a commitment to modify the DOI to include weekly calibration.

On 12/1/04 Discussions with Management were held and an FDA 483, Inspectional Observations was issued to Divya Patel, President. Mr. Patel stated that Amide would respond in writing to New Jersey District Office with planned corrective actions for all citations. Jasmine Shah, Director Regulatory Affairs, provided a list of fifteen promised corrective actions dated 12/1/04 **(Exh. 24)** in response to inspectional findings and discussions throughout the inspection. A recommendation for approval of ANDA 76-689, Mirtazapine OD Tablets, 15mg, 30mg, and 45mg was faxed to the New Jersey Preapproval Manager.

In addition to Divya Patel, President, the following firm officials were present at the exit meeting:

Ashok Nigalaye, Vice Scientific Affairs
Jasmine Shah, Director Regulatory Affairs
Daniel Bitler, Director Quality Assurance
Frank Carlucci, Ph.D., Director Quality Control
Ashesh Dave, Director Packaging
Mark Tenny, Director Manufacturing Operations
Satish Laroia, Director Manufacturing Compliance

FDA 483, INSPECTIONAL OBSERVATIONS

Quality System

1. **Changes are not consistently reviewed, approved and evaluated by the Quality Unit to determine the impact on marketed product or filing requirements. For example the following changes did not include**

evaluations of the impact on validation, stability or regulatory requirements:

During the inspection, I requested a summary of all changes logged for the past two years. Mr. Shah informed me that there was no centralized system or log of changes that had been implemented. He stated that each department may have one or more mechanisms to make a change and that they would be reviewed by the department and implemented as needed. I requested an example of each of the types of changes and associated documentation for each department. Approximately 7 different forms with different levels of review and approval were provided **(Exh. 25).** I asked Mr. Shah if the Quality Unit reviewed all changes, or was notified of all changes in a formalized manner. He stated that the change control documents had evolved as needed by each department and that there was currently no formalized system for the Quality Unit to look at all changes. He added that some of the forms require signature by the Quality Unit, however upon my review I noted that there was no requirement to evaluate the impact on stability, validation, or regulatory requirements on each form. We discussed the risk associated with not evaluating the collective changes that impact a marketed product and the potential issues associated with failing to meet filing requirements for changes. Mr. Shah stated that he understood the issue and that he would discuss the matter with the other members of management.

Change control forms included the following:

- In-process specification/sampling/testing approval sheet **(Exh. 25 p. 1)**
- Document history forms for procedural changes **(Exh. 25 p. 2)**
- In-process and finished product specification and method approval forms (including a revision log) **(Exh. 25 pp. 3-4)**
- Departmental Operating Instructions Revision Log **(Exh. 25 p. 5)**
- Raw material method/specification revision log **(Exh. 25 pp. 6-7)**
- Master production record request/change control form **(Exh. 25 pp. 8-9)**
- Change control log and problem reporting for Turbochrom **(Exh. 25 pp. 10-11)**

a. Raw Material Method/Specification Revision Log for Mirtazapine API describes the addition of a specification for bulk and tap densities and particle size.

An example of a change that had no documented evaluation of the impact on marketed product, stability, validation, or regulatory requirements was observed in the Raw Material Method/Specification Revision Log for Mirtazapine API used in the manufacture of the marketed product Mirtazapine Tablets and planned for use in ANDA 76-689, Mirtazapine Orally Disintegrating Tablets **(Exh. 26).** The change was described as, "Specification for bulk and tap densities and particle size were added. The tests are no longer for information only." There was no documentation of the specifications that were being implemented or reference to the data supporting the specifications. The particle size and bulk and tap densities were not discussed related to finished product quality. Although the one page document had an attached signature page which included signatures by the Directors of Quality Assurance and Regulatory Affairs as well as the Vice

President Operations, there was no documentation of what they were approving or what they had evaluated to determine whether the change should be implemented.

b. Quality Control Departmental Operating Instructions, (DOIs) which describe the use of commercial analytical testing equipment, (such as HPLCs, spectrophotometers, and FTIRs), contained handwritten changes and had attached notes stating, "Not in use".

During the initial walkthrough of the facility on 11/15/04, I reviewed several Departmental Operating Instructions (DOIs) in the Quality Control Laboratory that were maintained near each piece of analytical testing equipment. I noted a handwritten change on DOI QC-124, FTIR-8400 **(Exh. 27).** The DOI was written to describe calibration and operation of the Shimadzu FTIR. The equipment was recently used to test such finished products as Phentermine HCl Capsules, 30 mg seed formula, lot# 4022A and Phenazopyridine HCl Tablets 200mg, lot# 3715A. The DOI contained a handwritten crosscut in step 3 which noted, "Turn on the personal computer (PC), monitor and printer. Window 98 starts automatically." The handwritten notation changed 98 to NT and an additional note was added, "use the Password user for Name and #." The change was initialed and dated 2/4/02. The effective date of the DOI was 2/1/01. I asked Dr. Carlucci if manual changes to procedures were permissible. He stated that the changes should have been made formally, but that it was done some time ago. I asked how frequently the DOIs are reviewed and by whom. He stated that they are reviewed annually. He stated that he is currently in the process of reviewing them. The change was not reviewed by the Quality Unit or Dr. Carlucci, Director Quality Control.

Following the walkthrough and throughout the inspection I reviewed other DOIs that contained similar manual changes. For example DOI QC-074, Shimadzu HPLC System (Method Validation Studies), effective 3/3/93 **(Exh. 28)** had a manual crosscut in the title of the procedure to remove "(Method Validation Studies)." The change was dated 3/27/93; however the document was never formally revised, reviewed or approved by the Quality Unit.

Approximately 6 DOIs had attached post-it notes which said, "Not in use." The DOIs are as follows: QC-064, HPLC Fluorescence Detector **(Exh. 29),** QC-008, Diode Array Spectrophotometer **(Exh. 30),** QC-009, Atomic Absorption **(Exh. 31),** QC 010, IR Spectrophotmeter **(Exh. 32),** QC-010A, IR Spectrophotometer **(Exh. 33),** QC-013, Polarimeter **(Exh. 34).** Dr. Carlucci explained that some of the equipment was no longer in use or procedures had been modified and newer DOIs were in place. He stated that during his review he would remove any procedures which are no longer in use.

The DOIs are written and reviewed internally in the Quality Control Laboratory, but do not have the oversight or review of the corporate Quality Unit. Mr. Shah stated that a planned change for developing a system to manage change would include DOIs. Prior to the completion of the inspection, Ashok Nigalaye, Vice President Scientific Affairs stated that Amide would commit to developing a centralized change control system in which the Quality Unit would evaluate the impact of all changes for

marketed product to include evaluations of the impact on stability, validation and regulatory requirements. He stated that the approach and the system to be used would take some time to develop and implement, but that they would respond in writing with timeframes for promised corrections. Mr. Shah stated that he would also keep the District informed of the progress.

Laboratory Control System

2. **Quality Control laboratory supervisors, who review and approve raw material, in-process, finished product and stability data generated by the TurboChrom chromatography software, version 6.1.0, have manager access in TurboChrom and administrator access in Microsoft Windows NT version 4.00.1381, which permit alteration, deletion, renaming and relocation of raw data files. Additionally, audit trails containing remarks by the analyst are not currently reviewed.**

All analytical testing of raw materials, in-process and finished product for release and stability which requires HPLC analysis utilizes Turbochrom chromatography software, version 6.1.0 **(Exh. 35, 36).** Dmitriy Kalika, Information Technologist explained that Microsoft Windows NT version 4.00.1381 is the operating system which must be accessed in order to log onto the Turbochrom chromatography software. In the "Security Measures and Functions" section of DOI QC-111J, Turbochrom Client Server Data Security System **(Exh. 37 pp. 1-2),** it notes that the network data files protection prevents accidental and intentional file changes and deletion. All Turbochrom data is stored on the network file server..." Mr. Kalika stated that following logging onto NT with a unique username and password, a user must then log onto Turbochrom with a username and password. Each user has identified security or access privileges assigned in both NT and Turbochrom.

DOI QC-111J **(Exh. 37)** also notes that the following seven permissions are available in NT: Read, Delete, Execute, Write, Change Permission, Take Ownership, and Full Control. Permissions can be assigned to each directory or file. According to the DOI, "All Turbochrom users will have Read, Write and Execute privileges on files and folders which contain QC Lab analytical data. None of the Turbochrom users will have delete privileges on files and folders which contain QC Lab analytical data." The system was designed so that network login security prevents unauthorized users from gaining access to the network on which the Turbochrom Client Server resides.

According to Mr. Kalika, there are two levels of access used in Turbochrom; "Manager," which is the highest level and "User" which has less security privileges to prevent modification of methods **(Exh. 38).** Mr. Kalika stated that even the manager level of access which is needed to enter new methods by the laboratory supervisors does not permit alteration, deletion, modification, renaming or relocating of data files. He stated that in order the access raw data files, the user would have to access NT. Manoj Patel, Director Engineering is a System Administrator and was formerly employed full time. He still remains a System Administrator, but now only works at Amide approximately one day per week. He discussed the system with me via teleconference as he is located out of state. Mr. Patel stated that the highest level of NT access is Administrator. He explained that in his absence, Mr. Kalika also has Administrator access. I asked for a

list of any other employees currently assigned Administrator access. The list was provided as **Exh. 39.** It included Mr. Kalika but also noted three other employees, Frank Carlucci, Director Quality Control, Nilesh Patel, Supervisor Quality Control and Bharat Rana, Supervisor Quality Control. Manoj Patel explained that the additional administrators could only gain administrator access with the assistance of a second administrator logging in. I asked Nilesh Patel, Supervisor what responsibilities a supervisor has regarding raw data generated by analysts within his/her group for raw materials, in-process, finished product and stability testing. He stated that one of his responsibilities, and that of all the supervisors, is to review and approve the work of the analysts in his/her group. Dr. Carlucci, who also had administrator access, conducts review of data and assists in conducting laboratory investigations or resolving any testing issues that may arise.

I explained that due to the roles performed by the supervisors and Dr. Carlucci, which include the day to day review and approval of raw data resulting in the release of material, they should not have the ability to perform such functions as alteration, deletion, renaming and relocation of raw data files. Their current administrator access does not assure the security of the data on the system. Manoj Patel, Director Engineering and Jasmine Shah, Director Regulatory Affairs stated that they understood the concern and would make corrections immediately. Prior to the completion of the inspection, I was notified that all laboratory employees had been removed as system administrators. Documentation of the change was verified during the inspection and observed to be complete. Screen shots of administrator authorities were provided by Mr. Kalika **(Exh. 40).** He stated that only IT personnel would now have administrator access in NT. An example of Nilesh Patel's removed administrator access was provided as **Exh. 41.**

It was also noted during a walkthrough of the laboratory that the audit trail used in Turbochrom by analysts to document any problems, changes, or additional work are not routinely reviewed. As a corrective measure, a commitment to review the audit trail at the end of every analysis was made **(Exh. 24).**

Production System

3. **Research and Development (R&D) products are manufactured on commercial manufacturing equipment in the absence of cleaning validation studies. Cleaning verifications are not conducted following every R&D batch to assure the adequate removal of cross-contaminants prior to commercial manufacturing. For example:**

Review of equipment usage and cleaning logs in the production area during a walkthrough revealed that Research and Development (R&D) products, identified with "RBR" batch numbers, are manufactured on commercial manufacturing equipment. We discussed equipment cleaning and I requested documentation to show that cleaning verifications are conducted after each R&D batch, prior to manufacture of the next commercial product. Mr. Shah stated that verifications are not always conducted. He explained that other products which have been cleaned on the equipment may be used to demonstrate that the equipment is clean based on solubility. I stated that due to the lack of a completed cleaning validation for a research compound, and other attributes

than solubility that could impact cleaning such as toxicity and therapeutic dose, additional assurance should be provided that residuals from the research compound are not left on the equipment, potentially posing a risk to commercial product. Two examples were provided in which an R&D batch was manufactured on commercial equipment and cleaning verification was not conducted prior to manufacture of the next commercial batch.

a. **Amantadine HCl Capsules, R&D batch# RBR 2016 was manufactured in the double cone blender (id# 24) from 11/11/04 through 11/15/04. No cleaning verification was conducted prior to the manufacture of Chlordiazepoxide HCl and Clidinium Bromide Capsules, lot# 4647A on 11/17/04.**

Amantadine HCl Capsules are not approved. An R&D batch, # RBR 2016 was manufactured on the Tech Air double cone blender (equipment id# 24) on 11/11/04 through 11/15/04 **(Exh. 42).** The equipment was cleaned and "checked" visually on 11/17/04, however no swab or rinse samples were taken as a cleaning verification. On 11/17/04, a commercial lot of Chlordiazepoxide HCl and Clidinium Bromide Capsules, lot# 4647A was manufactured.

b. **Amantadine HCl Capsules, R&D batch# RBR 2016 was manufactured in the pony mixer (id# 4) from 11/11/04 through 11/15/04. No cleaning verification was conducted prior to the manufacture of Quinapril HCl 20mg Tablets, lot# 4674A on 11/16/04 through 11/17/04.**

Amantadine HCl Capsules, RBR# 2016 was also manufactured in the Day pony mixer from 11/11/04 through 11/15/04 **(Exh. 43).** The equipment was cleaned and "checked" visually on 11/16/04 prior to the commercial manufacture of Quinapril HCl Tablets, lot# 4674A on 11/16/04 through 11/17/04.

A justification document was provided as **Exh. 44** which states, "Similar equipments were used for the manufacture of Rimactane Capsules." However, no explanation was provided for how similar the processes (equipment) are. "Cleaning validation was performed for Rimactane Capsules with acceptable results." The report adds that Amantadine is more soluble than Rimactane in water and therefore cleaning validation for Rimactane can be applied to Amantadine Capsules. I stated that a matrix approach to cleaning could be used provided it was scientifically justified and that assurance was provided that worst case products and processes were being used to establish the matrix. We again discussed other attributes of a product, other than solubility that can be evaluated for cleaning validation purposes. We discussed the firm's practice of swabbing with water, despite the solubility of the product, and the use of a single cleaning agent for all products. Mr. Shah stated that they had not evaluated their cleaning practices recently and that as a corrective action and means of risk reduction they would be re-evaluated.

4. **Production documentation is not controlled in a manner to assure that it is not altered or removed. Partially executed production records are stored in common corridors outside the production rooms and are accessible to employees and contractors working in the facility even when the documents are not in use. Examples of in-process records observed in the common corridor include:**

During a walkthrough of the manufacturing area on 11/15/04, when production was not operational, I observed the storage of batch records in mounted file holders on the wall outside each production room. The records were in-process and had entries for the steps which had been completed. Because of numerous employees celebrating the Indian New Year, only a skeleton crew of employees was working. The in-process records had been left in the corridor since the last production day prior to the weekend. The manufacturing area was accessible to employees who were working as well as contractors who were observed working in the production area to meet a 12/15/04 deadline for operation of the expanded sugar coating area. Examples of the in-process records stored in an uncontrolled manner in the manufacturing corridors are as follows:

a. Betaxolol HCl 10mg Tablets, batch# 4660A (compression step# 3)

Betaxolol HCl 10mg Tablets, batch# 4660A was completed up to step# 3 of compression in the batch record. The weighing of filled containers of tablets was being conducted on 11/12/04, at which time the in-process record was stored outside the room **(Exh. 45).**

b. Meperidine HCl 100mg Tablets, batch# 4658A (compression step# 1)

Meperidine HCl 100mg Tablets, batch# 4658A, a schedule II narcotic, was completed through step#1 in preparation for compression of the tablets in production room #108 on 11/12/04. The partially executed record was outside the room **(Exh. 46).**

c. Amitex Pseudoephedrine Tablets, batch# 4667A (blending step# 15)

Amitex Pseudoephedrine Tablets, batch# 4667A was completed up to step# 15 in preparation for a blending step. Completion of step# 15 is documented on 11/12/04 (Friday). The record remained in the common manufacturing corridor on Monday 11/15/04 during the walkthrough **(Exh. 47).**

Mr. Shah stated that the records had been stored that way historically however he agreed with the need for better control of the manufacturing records. The following day he stated that a change in procedure to store the in-process records locked in the production room during non-production hours and during lunch and breaks would be implemented immediately. We discussed the protection that it provided to the product and company in complying with the GMPs. I observed the change in procedure during additional walkthroughs of the facility.

Facilities and Equipment System

5. **Approximately 25% of the commercial manufacturing equipment has not been qualified for its intended use. For example:**
   a. **Equipment id# 25, 7.5 ft.^{3} conical blender used to manufacture Dexchlorpheniramine Maleate 6mg Tablets, batch# 4636A**

The only qualification documentation available for equipment id# 25, 7.5 ft^3 conical blender was a single page equipment identification form **(Exh. 48).** The equipment was installed 6/90. The fixed speed blender was not qualified at that time and no qualification activities have been performed despite its routine use in production. For example, the blender was used to manufacture a commercial batch of Dexchlorpheniramine Maleate 6mg Tablets, batch# 4636A on 11/22/04. Other products recently manufactured using the blender are also included on the equipment usage and cleaning log **(Exh. 49).**

   b. **Equipment id# 29, 32.0 ft.^{3} conical blender used to manufacture Phenazopyridine HCl 95mg Tablets, batch# 4313A**

A single page equipment identification form was also the only equipment qualification documentation available for id# 29, 32.0 ft.^{3} Paterson-Kelly conical blender which was installed 2/92 **(Exh. 50).** The blender is used for the manufacture of Phenazopyridine HCl Tablets and was most recently used to manufacture a 95mg batch# 4313A on 6/18/04. Other batches of Phenazopyridine HCl Tablets manufactured on the equipment are documented in the equipment cleaning and use log **(Exh. 51).**

   c. **Equipment id# 26, 11.0 ft.^{3} conical blender used to manufacture Quinapril HCl and Hydrochlorthiazide Tablets, batch# 4700A**

A single page equipment identification form was also the only equipment qualification documentation available for id# 26, 11.0 ft.^{3} Tech Air conical blender which was installed 9/90 **(Exh. 52).** The blender was most recently used for the manufacture of Quinapril HCl and Hydrochlorthiazide Tablets, batch# 4700A on 11/29/04. Other products recently manufactured using the blender are also included on the equipment usage and cleaning log **(Exh. 53).**

Mr. Shah stated that the equipment was considered grandfathered and that it has been successfully used at the facility for many years, however he acknowledged the cGMP requirement for equipment to be qualified for its intended use. Mr. Shah stated that only upon my inquiry did they inventory the equipment and realize that such a large percentage of the equipment required qualification. He stated that they would develop a strategy for qualification of legacy equipment and added that current qualifications (as I noted during my review of other equipment) met current standards. Mr. Shah stated that their evaluation of the equipment revealed that approximately 25% of all manufacturing equipment did not have qualification documentation. He added that other more recently purchased equipment had various levels of qualification. He committed to

evaluating and correcting the missing or deficient documentation to assure that the equipment was demonstrated to be reliable for its intended use.

ANDA 76-689, Mirtazapine Orally Disintegrating Tablets, 15mg, 30mg, and 45mg

6. **There is no assurance that the equipment used in the manufacture of Mirtazapine Orally Disintegrating Tablets 15mg, 30mg, and 45mg is qualified for its intended use. For example:**

    a. **There was no operation or performance qualification for equipment id# 29, 32.0 ft.^{3} conical blender used to manufacture the final blend for the 220 kg batch size.**

(See also FDA 483 observation 5.)

The 32.0 ft.^{3} conical blender (equipment id# 29) used to manufacture the final blend for the 220 kilo master blend of Mirtazapine Orally Disintegrating Tablets has not been qualified for its operation or performance. The equipment, according to Mr. Shah is grandfathered and has been successfully used to manufacture other products, however there is no qualification documentation to support its use. An equipment identification form and executed installation qualification dated 12/11/95 were the only records available for review **(Exhs. 54, 55).**

    b. **The speed of equipment id# 38, 112.0 ft.^{3} conical blender was not evaluated during operation qualification and there was no protocol for operation and performance qualification to establish predetermined acceptance criteria.**

Review of the qualification documentation for equipment id# 38, the 112.0 ft.^{3} conical blender used for final blending of the 1000 kilo master blend of Mirtazapine Orally Disintegrating Tablets revealed that it was not evaluated for speed during the operation qualification (or during IQ or PQ) and does not have a protocol for either the operation or performance qualification to establish predetermined acceptance criteria **(Exh 56).** The initial qualification activities were conducted 6/16/99. Mr. Shah again stated that the equipment qualification program will be re-evaluated and additional testing and documentation will be performed as required.

    c. **There were no qualification protocols and no documented installation or operation qualification for equipment id# 51, Stokes B2 16 Station Tablet Press used for the manufacture of the finished tablets.**

The only equipment qualification that could be provided for equipment id# 51, the Stokes B2 16 Station Tablet press, used to manufacture Mirtazapine Orally Disintegrating Tablets, 15mg, 30mg, and 45mg, was an equipment identification form indicating that it was installed 5/83 **(Exh. 57)** and the evaluation of performance of the equipment following the manufacture of three production

batches of other products. There are no protocols and no documented installation or operation qualification for the equipment. Mr. Shah stated that based on the age of the equipment it was considered grandfathered. He stated that as a corrective action the equipment would undergo qualification, however he noted that it had been successfully used for many years. We agreed that to assure consistency and reproducibility of the equipment, it should be qualified for its intended use.

Mr. Shah added that following the evaluation of the 25% of unqualified equipment, their review revealed that an additional 27% of the equipment required supplemental qualification, 34% had protocols with memos, and only approximately 14% met current qualification standards. He and Dr. Nigayale acknowledged the deficiency stating that plans to correct would be submitted in writing. Dr. Nigayale mentioned his concern with qualifying equipment that was currently unsupported by the vendor due to its age. Mr. Patel stated that they would be gradually replacing equipment as they transition products to their newer facilities.

Attachments

- FDA 482, Notice of Inspection, dated 11/15/04, 1p.
- FDA 483, Inspectional Observations, dated 12/1/04, 2pp.
- Pre-approval assignment for ANDA 76-689, Mirtazapine Orally Disintegrating Tablets, 15mg, 30mg, and 45mg, 2pp.
- SAN-DO Complaint# 24455, 4pp.
- DQRS reports (7), 14pp.
- NDA Final Field Alert Report for NDA 40-282, Digoxin Tablets, 11pp.
- Profile sample CR# 68868 (including FDA 484, Receipt for Samples)

Exhibits

1. Organizational Chart, 18pp.
2. Product List, 8pp.
3. Controlled substance list and associated products, 2pp.
4. Facility diagrams, 2pp.
5. Manufacturing equipment list, 20pp.
6. Consultant List, 1p.
7. List of CBEs and PASs, 3pp.
8. Labeling for "DESI/grandfathered" products with extended release patterns, 5pp.
9. Interim development report written by Kali Laboratories, Inc., 28pp.
10. Executed batch record for Mirtazapine Orally Disintegrating Tablets, master blend, batch# 1294, 21pp.
11. Executed batch record for Mirtazapine Orally Disintegrating Tablets, 15mg, batch# 1295, 11pp.
12. Executed batch record for Mirtazapine Orally Disintegrating Tablets, 30mg, batch# 1299, 11pp.
13. Executed batch record for Mirtazapine Orally Disintegrating Tablets, 45mg, batch# 1300, 13pp.
14. Release and stability specifications for Mirtazapine Orally Disintegrating Tablets, 4pp.
15. Stability Summary Tables for Mirtazapine Orally Disintegrating Tablets 45mg, 4pp.

Amide Pharmaceutical, Inc.
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EI: 11/15-19, 23, 24, 29, 12/1/04 EDM

16. Stability Summary Tables for Mirtazapine Orally Disintegrating Tablets 15mg, 4pp.
17. Stability Summary Tables for Mirtazapine Orally Disintegrating Tablets 30mg, 4pp.
18. Amide Product Development Summary Table, 1p.
19. Complaint summary log for 2003 and 2004, 2pp.
20. Amidrine Package Insert, 1p.
21. Quarantine raw material sampling booth cleaning verification log, 1p.
22. Room and equipment cleaning and usage logs for compression room 115, 3pp.
23. Digoxin Tablets, 0.125mg Annual Product Review, dated 3/23/04, 17pp.
24. List of corrective action commitments, dated 12/1/04, 1p.
25. Departmental change control forms, 11pp.
26. Raw material method/specification revision log, 2pp.
27. DOI QC-124, FTIR-8400, Rev. 00, dated 2/1/01, 4pp.
28. DOI QC-074, Shimadzu HPLC System, Rev. 01, dated 3/3/93, 4pp.
29. DOI QC-064, HPLC Fluorescence Detector, Rev. 00, dated 8/25/92, 2pp.
30. DOI QC-008, Diode Array Spectrophotometer, Rev. 02, dated 1/15/96, 7pp.
31. DOI QC-009, Atomic Absorption, Rev. 02, dated 9/29/98, 3pp.
32. DOI QC-010, IR Spectrophotometer, Rev. dated 9/29/98, 4pp.
33. DOI QC-010A, IR Spectrophotometer, Rev. 00, dated 9/29/98, 4pp.
34. DOI QC-013, Polarimeter, Rev. 02, dated 9/29/98, 2pp.
35. List of computerized instruments, 1p.
36. Screen shot of Windows NT version 4.00.1381, 1p.
37. DOI QC-111J, Turbochrom Client Server Data Security System, dated 10/6/98, 4pp.
38. Turbochrom manual including job types and access levels, 6pp.
39. Personnel with administrator access, 1p.
40. Administrator functionalities in Windows NT, 10pp.
41. Screen shot of Nilesh Patel's access in Windows NT, 1p.
42. Equipment usage and cleaning log for equipment id.# 24, 1p.
43. Equipment usage and cleaning log for equipment id.# 4, 1p.
44. Justification for cleaning evaluation for Amantadine Capsules, dated 11/15/04, 2pp.
45. Betaxolol HCl Tablets, batch# 4660A, portion of batch record, 1p.
46. Meperidine HCl Tablets, batch# 4658A, portion of batch record, 3pp.
47. Amitex PSE Tablets, batch# 4667A, portion of batch record, 8pp.
48. Equipment Identification form for id# 25, 1p.
49. Equipment usage and cleaning log for equipment id.# 25, 2pp.
50. Equipment Identification form for id# 29, 1p.
51. Equipment usage and cleaning log for id.# 29, 2pp.
52. Equipment Identification form for id# 26, 1p.
53. Equipment usage and cleaning log for equipment id.# 26, 2pp.
54. Equipment Identification form for id# 29, 1p.
55. Installation Qualification Report for id.# 29, dated 12/11/95, 7pp.
56. Equipment Qualification Report for id.# 38, dated 6/16/99, 16pp.
57. Equipment Identification form for id.# 51, 5pp.

Erin D. McCaffery, CSO
New Jersey District